UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,405	07/24/2002	Baskaran Chandrasekar	3521-101	2963

6449 7590 09/06/2007

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
09/06/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/088,405	CHANDRASEKAR ET AL.	
	Examiner	Art Unit	
	Kendra D. Carter	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-14,16-18 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-14,16-18 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of June 5, 2007 made to the office action filed December 5, 2006. Claims 1, 3-8, 10-14, 16-18 and 20-24 are pending in the application and are being examined on the merits herein. Claims 2, 9, 15, and 19 are cancelled and claim 24 is new. Claims 1, 3-7 and 16-17 are amended.

In light of the amendments, the 35 U.S.C. 103(a) of claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-23 as being unpatentable over Ungs (U.S. 5,866,561) is withdrawn.

In light of the amendments, the 35 U.S.C. 103(a) of claims 5-7, 11 and 21 as being unpatentable over Ungs (U.S. 5,866,561) and further in view Pitha (U.S. 4,727,064) is withdrawn.

Due to the amendment to the claims, the new 35 U.S.C. 103(a) rejections are made below.

The applicant's arguments are addressed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 recites the limitation "therapeutic moiety", which is dependent on claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs (U.S. 5,866,561) in view of O'Brien et al. ("Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions", J. Am. Coll. Cardiol., November 1996, vol.

28(5), pp. 111-8) in further view of Bauters et al. ("The biology of restenosis", Prog. Cardiovas. Dis., Sept-Oct. 1997, vol. 40(2), pp. 107-116).

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that restenosis following PTCA is a signification problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site, i.e. one that has been injured by PTCA. Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claims 1 and 14. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta estradiol, as recited in claims 8 and 18, as Ungs teaches the compound can be administered via a stent or balloon catheter. There is no other therapeutic moiety

disclosed that can be administered other than the estrogen compound, preferably 17-β estradiol or estradoil (see column 4, lines 1, 10 and 11; claim 1; addresses claim 24).

Ungs does not specifically teach a method of improving reendothelization and vascular endothelial function. Ungs also does not specifically teach administering 17β-estradiol in the specific dosages in an amount effective to improve reendothelization and vascular endothelial function as recited in claims 1, 3-4 and 16-17.

O'Brien et al. teaches estrogen replacement therapy has been associated with a reduction in cardiovascular events and improvement in endothelial function (see abstract, background, lines 1-3). The results of the study suggest that estrogen replacement therapy reduces restenosis after coronary intervention, particularly in patients receiving directional coronary atherecotomy (see page 1117, column 1, conclusion, lines 1-4). In addition, estrogen may prevent restenosis by altering cellular migration and neointimal proliferation after coronary intervention (see page 115, column 2, paragraph 3, lines 1-3). In vitro, physiologic levels of estrogen have been shown to inhibit proliferation of vascular smooth muscle from the coronary arteries of female pigs (see page 115, column 2, paragraph 3, lines 5-6 to page 1116, column 1, line 1).

Bauters et al. teaches that previous investigations have underscored the principle of cross-talk between endothelial cells and smooth muscle cells. Neointimal

thickness is closely related to the presence of a regenerated endothelium. Indeed, intimal areas that are rapidly covered by continuous endothelium are protected from the accumulation of intimal SMCs (smooth muscle cells), whereas typical intimal hyperplasia occurs in areas where re-endothelialization is delayed. Endothelium, in addition to its well-known role in regulating vessel tone and platelet aggregation, appears to modulate proliferative activity of the underlying SMCs (see page 108, column 2, growth regulatory properties of endothelial cells, lines 1-13). Dysfunctional regenerating endothelium may contribute to the development of thickened intima because of SMC proliferation. There are documented cases that demonstrate retardation of endothelial cell recoverage over damaged as opposed to normal media (see page 109, column 1, lines 3-11).

Although Ungs does not specifically teach a method of improving reendothelization, Ungs teaches a reduction in restenosis. O'Brien et al. also teaches the effect of estrogen such as estrogen replacement therapy (i.e. such as 17β estradiol and its derivatives) on reducing restenosis after injury. O'Brien et al. also teaches some of the mechanistic properties of estrogen in the reduction of restenosis, by inhibiting proliferation of vascular smooth muscle from the coronary arteries. Bauters et al. teaches the connection between restenosis/smooth muscle proliferation and reendothelization, in that there is a cross-talk between endothelial cells and smooth muscle cells. Particularly, neointimal thickness is closely related to the presence of a

regenerated endothelium. Indeed, intimal areas that are rapidly covered by continuous endothelium are protected from the accumulation of intimal SMCs (smooth muscle cells), whereas typical intimal hyperplasia occurs in areas where re-endothelialization is delayed (see page 108, column 2, growth regulatory properties of endothelial cells, lines 1-13). Dysfunctional regenerating endothelium may contribute to the development of thickened intima because SMC proliferation. There are documented cases that demonstrate retardation of endothelial cell recoverage over damaged as opposed to normal media (see page 109, column 1, lines 3-11). In other words, since restenosis is reduced by the inhibition of proliferation of SMCs as taught by O'Brien et al., and the proliferation of SMC's are related to the dysfunctional regenerating endothelium (i.e. reendothelialization) as taught by Bauters et al., then one of ordinary skill in the art would find it obvious to treat a patient with 17β estradiol or its derivatives to improve reendothelialization since Ungs discloses that 17β estradiol reduces restenosis as well as O'Brien discloses that estrogen reduces restenosis.

In regards to improving vascular endothelial function, the above argument applies. Particularly, O'Brien et al. teaches the relationship between estrogen replacement therapy and its known ability to improve endothelial function (see abstract, background, lines 1-3). Since 17β estradiol and its derivatives are known in the art to be used as estrogen replacement therapy, it is obvious that one skilled in the art would administer 17β estradiol to improve vascular endothelial function.

Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that instantly claimed, and to reduce the incidence of restenosis following a treatment such as PTCA that induces vascular injury, it is considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function in a patient having suffered vascular injury, as recited in the claim.

In regards to the amounts of 17β estradiol or its derivatives as disclosed in claims 1, 3-4, and 16-18, it is noted that Ungs teaches that 17β-estradiol is a preferred estrogen compound (see column 4, liens 1-11,, in particular), and Ungs also teaches various methods of application of the estrogen via catheters, stents, etc, and refers to prior art catheter, for example, that are used for the local administration of drugs (see column 3, lines 1-15, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of 17β-estradiol provided in the method, according to the guidance provided by Ungs, to provide the desired treatment, such as the desired reduction in restenosis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 12-13 and 22-23, Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Regarding claims 10 and 20, Ungs teaches that the estrogen can be administered with an ionic carrier (pharmaceutically acceptable carrier) in an iontophoresis method using delivery balloon catheter (see column 2, lines 32-40, in particular.)

(2) Claims 5-7, 11 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs (U.S. 5,866,561) in view of O'Brien et al. ("Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions", J. Am. Coll. Cardiol., November 1996, vol. 28(5), pp. 111-8) in further view of Bauters et al. ("The biology of restenosis", Prog. Cardiovas. Dis., Sept-Oct. 1997, vol. 40(2), pp. 107-116) as applied to claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-24 above, and further in view of Pitha (U.S. 4,727,064).

Ungs, O'Brien et al. and Bauters et al. teachings are as applied to claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-24 above.

Ungs in view of O'Brien et al. and in further view of Bauters et al. does not specifically teach administration of hydroxypropyl-beta-cyclodextrin (HPCD) as recited in claims 5-7. Ungs in view of O'Brien et al. and in further view of Bauters et al. also does not specifically teach providing a pharmaceutically acceptable carrier in administering the 17-beta estradiol via stent, as recited in claims 11 and 21.

Pitha teaches that pharmaceutical preparations containing cyclodextrin derivatives have enhanced dissolution properties and thus enhanced absorption by the body (see abstract, in particular.) Pitha teaches that cyclodextrin mixtures effectively solubilize liphophilic drugs in aqueous media (pharmaceutically acceptable carrier), and have low toxicity (see column 2, lines 35-60, in particular.) Pitha demonstrates that estradiol is a drug that exhibits improved solubility in combination with hydroxypropyl-beta-cyclodextrin (see Table I, in particular.) Accordingly, Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media, as recited in claims 11 and 21 are known.

Regarding the dosage amount recited in claim 7, Pitha teaches that the cyclodextrin additives may generally be utilized in a weight percent of from about 40-

60% of the drug solution (see column 2, lines 62-68, in particular.) Pitha furthermore teaches intraperitoneal injection of hydroxypropyl-beta-cyclodextrin into mice was non-fatal at 3.2g/kg, and teaches a lack of oral toxicity of the hydroxypropyl-beta-cyclodextrin (see column 4, line 64 through column 5, line 5, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize the amount of hydroxypropyl-beta-cyclodextrin provided in the medication, according to the guidelines provided by Pitha, to provide the desired solubility and absorption characteristics of the estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the hydroxypropyl-beta-cyclodextrin and pharmaceutically acceptable carrier of Pitha in the 17-beta estradiol delivery method of Ungs, with the expectation of improving the solubility and absorption of the 17-beta estradiol compound in the patient.

(3) Claims 1, 3-4, 8, 10-14, 16-18, 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs (U.S. 5,866,561) in view of Fontana (US 5,383,332) in further view of Grainger et al. (US 6,117,911).

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that restenosis following PTCA is a signification problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site, i.e. one that has been injured by PTCA. Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claims 1 and 14. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta estradiol, as recited in claims 8 and 18, as Ungs teaches the compound can be administered via a stent or balloon catheter. There is no other therapeutic moiety disclosed that can be administered other than the estrogen compound, preferably 17-β estradiol or estradoil (see column 4, lines 1, 10 and 11; claim 1; addresses claim 24).

Ungs does not specifically teach a method of improving reendothelization and vascular endothelial function. Ungs also does not specifically teach administering 17β-estradiol in the specific dosages in an amount effective to improve reendothelization and vascular endothelial function as recited in claims 1, 3-4 and 16-17.

Fontana teaches administering an effective amount of estradiol dervivatives used in the method of inhibiting aortal smooth muscle cell proliferation, particularly restenosis, in humans (see abstract). The effective amount means an amount of compound of the methods of the present invention which is capable of inhibiting the symptoms of the pathological conditions herein described (see column 5, lines 13-16). The compounds are administered after medical procedures such as angioplasty (see column 5, lines 11 and 12). The compound is combined with a pharmaceutically acceptable carrier from 0.1% to 99.9% by weight of the formulation (see column 5, lines 35-39).

Grainger et al. teaches compounds to treat vascular traumas of differing severity, such as to prevent vascular rejection following graft or transplant, while larger doses are sufficient to treat more extensive vascular trama, such as restenosis following angioplasty (see column 34, lines 4-10). A biodegradable stent with the therapeutic agent impregnated therein can further be coated with a biodegradable coating having the therapeutic agent dispersed therein (see column 38, lines 27-30). Intravascular stents also provide a mechanical means of providing an increase in luminal area of a vessel (see column 38, lines 36-38). Furthermore, the placement of intravascular stents

comprising a therapeutic agent which is an inhibitor of smooth muscle cell proliferation can provide increased efficacy by reducing or preventing intimal proliferation. This inhibition of intimal smooth muscle cells and stroma produced by the smooth muscle and pericytes can allow more rapid and complete re-endothelization following the intraventional placement of the vascular stent. The increased rate of re-endothelization and stabilization of the vessel wall following stent placement can reduce the loss of luminal area and decreased blood flow which is the primary cause of vascular stent failures (see column 38, liens 39-50).

Although Ungs does not specifically teach a method of improving reendothelization and vascular endothelial function, Ungs teaches 17β-estradiol reduces restenosis. Fontana teaches that estrogen derivatives reduces restenosis and particularly inhibits aortal smooth muscle cell proliferation. Grainger et al. provides the teaching to connect restenosis, smooth muscle cell proliferation and improving reendothelization and vascular endothelial function. Thus, a method of improving reendothelization and vascular endothelial function is rendered obvious by Ungs in view of Fontana and in further view of Grainger et al.

Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that instantly claimed, and to reduce the incidence of

restenosis following a treatment such as PTCA that induces vascular injury, it is considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function in a patient having suffered vascular injury, as recited in the claim.

In regards to the amounts of 17β estradiol or its derivatives as disclosed in claims 1, 3-4, and 16-18, it is noted that Ungs teaches that 17β-estradiol is a preferred estrogen compound (see column 4, liens 1-11, in particular), and Ungs also teaches various methods of application of the estrogen via catheters, stents, etc, and refers to prior art catheter, for example, that are used for the local administration of drugs (see column 3, lines 1-15, in particular.) Additionally, Fontana teaches that estradiol derivatives are effective to reduce restinosis in an amount from 0.1% to 99.9% by weight of the formulation (see column 5, lines 35-39). Therefore in light of the discussion above, the amounts would be obvious to one skilled in the art. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of 17β-estradiol provided in the method, according to the guidance provided by Ungs, to provide the desired treatment, such as the desired reduction in restenosis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 11 and 21, the use of a stent coated with said 17β-estradiol, and a phraceutically acceptable carrier is obvious because Grainger et al. teaches that the placement of intravascular stents comprising a therapeutic agent which is an inhibitor of smooth muscle cell proliferation can provide increased efficacy by reducing or preventing intimal proliferation. This inhibition of intimal smooth muscle cells and stroma produced by the smooth muscle and pericytes can allow more rapid and complete re-endothelization following the intraventional placement of the vascular stent. The increased rate of re-endothelization and stabilization of the vessel wall following stent placement can reduce the loss of luminal area and decreased blood flow which is the primary cause of vascular stent failures (see column 38, liens 39-50). Thus, the limitation of claim 21 is taught.

Regarding claims 12-13 and 22-23, Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Regarding claims 10 and 20, Ungs teaches that the estrogen can be administered with an ionic carrier (pharmaceutically acceptable carrier) in an iontophoresis method using delivery balloon catheter (see column 2, lines 32-40, in particular.)

(4) Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs (U.S. 5,866,561) in view of Fontana (US 5,383,332) in further view of Grainger et al. (US 6,117,911), and further in view of Pitha (U.S. 4,727,064).

Ungs, Fontana and Grainger et al. teachings are as applied to claims 1, 3-4, 8, 10-14, 16-18, 20-24 above.

Ungs in view of Fontana and in further view of Grainger et al. does not specifically teach administration of hydroxypropyl-beta-cyclodextrin (HPCD) as recited in claims 5-7.

Pitha teaches that pharmaceutical preparations containing cyclodextrin derivatives have enhanced dissolution properties and thus enhanced absorption by the body (see abstract, in particular.) Pitha teaches that cyclodextrin mixtures effectively solubilize liphophilic drugs in aqueous media (pharmaceutically acceptable carrier), and have low toxicity (see column 2, lines 35-60, in particular.) Pitha demonstrates that estradiol is a drug that exhibits improved solubility in combination with hydroxypropyl-

beta-cyclodextrin (see Table I, in particular.) Accordingly, Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media are known.

Regarding the dosage amount recited in claim 7, Pitha teaches that the cyclodextrin additives may generally be utilized in a weight percent of from about 40-60% of the drug solution (see column 2, lines 62-68, in particular.) Pitha furthermore teaches intraperitoneal injection of hydroxypropyl-beta-cyclodextrin into mice was non-fatal at 3.2g/kg, and teaches a lack of oral toxicity of the hydroxypropyl-beta-cyclodextrin (see column 4, line 64 through column 5, line 5, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize the amount of hydroxypropyl-beta-cyclodextrin provided in the medication, according to the guidelines provided by Pitha, to provide the desired solubility and absorption characteristics of the estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the hydroxypropyl-beta-cyclodextrin and pharmaceutically acceptable carrier of Pitha in the 17-beta estradiol delivery method of

Ungs in view of Fontana and in further view of Grainger et al., with the expectation of improving the solubility and absorption of the 17-beta estradiol compound in the patient.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been fully considered.

> The Applicant argues the *Hirao* and *Kropa* cases cited in the pending Action do not support the position that reduction of restenosis is not entitled to patentable weight.

In light of the amendment to the claims, the Examiner agrees because the present claims are clear to read on a method of improvement of reendothelization and vascular endothelial function.

> The Applicant argues that Ungs' solution to the problem is not to administer a 17-β estradiol in an amount effective to reduce restenosis to the site of dialation, but instead to avoid PTCA altogether. Therefore, Ungs teaches away from applicant's solution. Ungs states at column 1, lines 49-51 that "[a]dministration of estrogen to the stenosed, dilated region after PTCA has thus been suggested for the purposes of preventing restenosis," one would recognize that statement to be based not on any of Ungs' work, but simply a summary statement regarding the prior art disclosed in the Ungs patent. Thus, one of ordinary skill would not read Ungs to suggest that a 17β-estradial alone can improve reendothelization and vascular endothelial function one of ordinary skill.

> Since the use of a 17-β estradiol as claimed is not suggested by Ungs, the particular dose ranges discovered by the applicant are likewise inventive.

The Examiner disagrees because first, the statement, administration of estrogen to the stenosed, dilated region after PTCA has thus been suggested for the purposes of preventing restenosis, is a teaching as a whole of what is known in the art. Second, Ungs teaches administering the same compound via the same method as that instantly claimed, and to reduce the incidence of restenosis following a treatment such as PTCA that induces vascular injury, it is considered that the method of Ungs would necessarily also reduce restenosis in a patient having suffered vascular injury, as recited in the claim. Therefore, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.) Accordingly, it is considered that one of ordinary skill in the art would have found it obvious to vary/and or optimize the amount of the estradiol provided, such as to achieve the amounts as claimed, with the expectation of providing a suitable treatment method. Since the amendment of the claims, the method of the improvement of reendothelization and vascular endothelial function is given patentable weight and is addressed in the above office action.

> The Applicant argues that the Stack Declaration of record reiterates that prevention of restenosis requires the inhibition of smooth muscle cell proliferation, as well as the promotion of vessel regeneration and repair. Further, that a compound may be known as capable of reducing proliferation of smooth muscle cells would not lead one to predict that such compound would also promote reendothelialization. Dr. Stack

> provides examples of compounds that inhibit proliferation, but no not promote reendothelization. The field is unpredictable, and the use of a 17-β estradiol as presently claimed would not have been suggested by Ungs. Ungs does not suggest the alleged inherent feature, and the Stack Declaration is further evidence that one would not have expected a 17-β estradiol to have the presently claimed effect. Moreover there is no evidence in Ungs that the presently claimed dose of estrogen was ever actually administered, likewise undercutting any inherency argument.

The Examiner disagrees because first, the new 35 USC 103(a) rejections address the limitation of the improvement of reendothelization and vascular endothelial function by administering 17β-estradiol or its derivatives. Second, since Ungs teaches administering the same compound via the same method steps as those instantly claimed, it is considered that the method of Ungs also necessarily improves reendothelization and vascular endothelial function. Third, the fact that applicant has recognized another advantage which would flow naturally from following the teachings or suggestion of the prior art cannot be the basis for patentability when the prior art teaches the invention or when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Fourth, actual proof that the estrogen compound was actually administered, such as through examples, is not required by the prior art.

> The Applicant argues that Pitha does not remedy the defects in Ungs. Pitha is not combinable with Ungs. There is noting in Pitha about the applicability of its teachings in the context of PTCA or coated stents.

The Examiner disagrees because Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-

cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media are known. The limitation of PTCA and coated stents are taught by Ungs. Particularly, Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by *coating a stent with an estrogen compound* or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular). Ungs also teaches that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KDC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER